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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,739	11/18/2003	Murugan R. Pandian	A-1789div	6774

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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 08/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/716,739	PANDIAN ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-25 and 42-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-25 and 42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The amendment filed June 6, 2005 is acknowledged and has been entered.

Claim Objections

1. Claim 23 is objected to because of the following informalities: Claim 23, line 21 the recitation "in the the samples" should be --in the samples--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 23-25 and 42-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. On page 2, lines 22-28 in the specification. The applicant discloses a method for detecting a trophoblastic disease in a subject comprising the steps of a) contacting a biological sample from the subject with antibodies that specifically bind ITA and hCG in one assay,; b) confirming that the subject is not pregnant; and c) comparing the amounts of ITA and hCG in the sample to standard ITA and hCG amounts obtained from a population of normal subjects. A

higher amount of ITA **and** hCG in the sample as compared to the standards indicates the presence of a trophoblastic disease. On page 17, lines 25-30 in the specification, the Applicant discloses that ITA can be measured as a multiple of medians (MoM). The ITA measured in a sample can be compared to the 50th percentile of the ITA values for a population of normal pregnant women or normal subjects. If the ITA value of the sample is greater that the 50th percentile, there would be a significant chance that the woman is pregnant, the fetus of the pregnant mother has Down's syndrome, or that the woman has a trophoblastic disease. The Applicant does not disclose a method of detecting trophoblastic disease wherein confirming that the subject is not pregnant; comparing the determined amount of hyperglycosylated human chorionic gonadortropin present in the sample to a 50th percentile of amounts of hyperglycosylated human chorionic gonadotropin present in sample obtained from subject who do not have a trohpoblastic disease; and comparing the determined amount of human chorionic gonadotropin present in he sample to a 50th percentile of amounts of human chorionic gonadotropin present in samples obtained from subjects who do not have a trophoblastic disease, wherein an amount of hyperglycostylated human chorionic gonadotropin or an amount of human chorionic gonadotropin present in the sample which is greater than the 50th percentile of the amounts of hyperglycosylated human chorionic gonadotropin or human chorionic gonadotropin present in the samples obtained from subjects who do not have a trophoblastic disease, respectively, indicates the presence of a trophoblastic disease. There is no description in the specification disclosing a method of detecting trophoblastic disease wherein confirming that the

subject is not pregnant; comparing the determined amount of hyperglycosylated human chorionic gonadortropin present in the sample to a 50th percentile of amounts of hyperglycosylated human chorionic gonadotropin present in sample obtained from subject who do not have a trohpoblastic disease; and comparing the determined amount of human chorionic gonadotropin present in he sample to a 50th percentile of amounts of human chorionic gonadotropin present in samples obtained from subjects who do not have a trophoblastic disease, wherein an amount of hyperglycostylated human chorionic gonadotropin or an amount of human chorionic gonadotropin present in the sample which is greater than the 50th percentile of the amounts of hyperglycosylated human chorionic gonadotropin or human chorionic gonadotropin present in the samples obtained from subjects who do not have a trophoblastic disease, respectively, indicates the presence of a trophoblastic disease.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 is vague and indefinite because it contradicts claim 23. Claim 23 requires a confirmation step that the subject is not pregnant. However, claim 25 requires that the trophoblastic disease is a hydatidiform mole which is known to be a pathologic condition of pregnancy (see definition of hydatidiform mole on attached

sheet). Therefore, it is unclear how one can detect a pathologic condition of pregnancy when the subject is confirmed to be not pregnant.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 23-25, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cole et al (Clinical Chemistry 47:2, 308-315, Feb. 2001) in view of O'connor et al (US 6,500,627) in light of Birken et al (Immunochemical measurement of Early Pregnancy Isofoms of hCG: Potential Applications to Fertility Research, Prenatal Diagnosis, and Cancer, 32 (2001) 635-643) in view of Hochstrasser et al (US 2003/0157580) and Birken et al (US 6,521,416).

Cole et al disclose human chorionic gonadotropin immunoassays in the diagnosis of trophoblastic diseases. Cole et al disclose that patients with trophoblastic disease produce ordinary and irregular forms of human chorionic gonadotropin (p. 308). Cole et al disclose that trophoblastic disease include complete and partial hydatidiform mole, postmolar tumor, gestational choriocarcinoma, testicular choriocarcinoma, and placental site trophoblastic disease (p. 309). Cole et al discloses that patients can be diagnosed with choriocarcinoma solely from a persistent positive hCG result, in the absence of a pregnancy (p. 314). Cole et al is generic with respect to the reagents used in the immunoassay.

Cole et al differ from the instant invention in failing to specifically state the use of antibodies to the hyperglycosylated human chorionic gonadotropin and human chorionic gonadotropin and also fails to labels in the immunoassay in one assay.

O'Connor et al (US 6,500,627) disclose methods of detecting trophoblastic disease. O'Connor et al disclose that the trophoblastic disease can include choriocarcinoma or hydatidiform mole. O'Connor et al disclose contacting a sample from a subject with an antibody which specifically binds to a molecular isoform of hCG.

O'Connor et al disclose contacting the sample with a second antibody which specifically binds to intact non-nicked hCG (hCG) (col 4 and col 25-26). O'Connor et al disclose B152 antibodies specific for the isoform of hCG (col 10, lines 40-44). Birken et al (Archives of Medical Research, 2001, 635-643) disclose that B152 is hyperglycosylated form (abstract). Therefore, O'Connor et al teaches detecting hyperglycosylated hCG. O'Connor et al disclose that the amount of B152 isoform (hyperglycosylated hCG) and hCG are increased in trophoblast disease (col 25-26). O'Connor et al also disclose that hCG is elevated in pregnancy. O'Connor et al discloses that the sample can be a blood or urine sample. O'Connor et al disclose that detection can be performed by using an labeled antibody. O'Connor et al disclose that the label can be a radioactive isotope such as I^{125}.

It would have been obvious to one of ordinary skill in the art to incorporate antibodies and labels as taught by O'connor et al into the method of diagnosing as taught by Cole et al because Cole et al specifically teaches that immunoassays are used for diagnosing trophoblastic disease and O'connor et al teaches specific antibodies and labels used in immunoassays for diagnosing trophoblastic disease. Therefore, one of ordinary skill in the art would have a reasonable expectation of success incorporating antibodies and labels as taught by O'connor et al into the method of Cole et al.

Cole et al and O'connor et al fail to teach confirming the subject is not pregnant. Cole et al and O'connor et al also differs from the instant invention in failing to teach comparing the determined amount of hyperglycosylated human chorionic gonadotropin

present in the sample to sample obtained from subjects who do not have a trophoblastic disease and comparing the determined amount of human chorionic gonadotropin present in the sample to amounts obtained from subjects who do not have a trophoblastic disease.

Since Cole et al specifically teaches that non-pregnant subjects can be diagnosed with trophoblastic disease and also since the combination of Cole et al and O'Connor et al disclose that hyperglycosylated hCG and hCG are elevated in both trophoblastic disease and pregnancy one of ordinary skill in the art would consider that pregnancy would have to be excluded before determining trophoblastic disease and thus would confirm that the patient was not pregnant before determining trophoblastic disease. Further, Hochstrasser et al (abstract & page 1, paragraph 0012) teaches that in order to perform diagnostic assays on markers which are known to be involved in more than one condition, one must be able to distinguish between the two conditions and thus perform an assay to exclude one of the conditions. Therefore, it would have been obvious to one of ordinary skill in the art to confirm that the subject is not pregnant before detecting a trophoblastic disease.

Birken et al (US 6,521,416) discloses that analysis of the metabolites of gonadotropins in a sample can help to distinguish between healthy and abnormal physiological states. Birken et al (US 6,521,416) discloses thresholds to determine abnormal states (col 2, line 54 – col 3 , line 14). Birken et al disclose comparing the sample to normal subjects to determine the abnormal state.

It would have been obvious to one of ordinary skill in the art to incorporate thresholds and samples from normal subjects as taught by Birken et al (US 6,521,416) into the modified method of Cole et al because Birken et al shows that this provides for the analysis of the metabolites of gonadotropins in a sample to distinguish between healthy and abnormal physiological states.

With respect to the a 50th percentile as recited in the instant claims, the optimum threshold in this case 50th percentile can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. Further, it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation ." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Also, one of ordinary skill in the art would optimize the assay to minimize the false positive and false negative results.

10. Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cole et al (Clinical Chemistry 47:2, 308-315, Feb. 2001) and O'connor et al (US 6,500,627) in light of Birken et al (Immunochemical measurement of Early Pregnancy Isofoms of hCG: Potential Applications to Fertility Research, Prenatal Diagnosis, and Cancer, 32

(2001) 635-643) in view of Hochstrasser et al (US 2003/0157580) and Birken et al (US 6,521,416) as applied to claims 23-25, 42 and 43 above, and further in view of Campbell et al (US 4,946,958).

See above for teachings of Cole et al., O'Connor et al., Hochstrasser et al and Birken et al.

Cole et al., O'Connor et al., Hochstrasser et al and Birken et al differ from the instant invention in failing to teach the assay is a chmiluminescent sandwich assay.

Campbell et al disclose a chemiluminescent label which is conveniently linked to a monoclonal antibody or other protein and is used in immunoassay for the quantitation of an antigen of interest (abstract). Campbell et al disclose that the use of this chemiluminescent label in assays provides a means of improving the sensitivity of measurement of proteins and polypeptides by one to two orders of magnitude (col 7, lines 27).

It would have been obvious to one of ordinary skill in the art to substitute the chemiluminescent label as taught by Campbell et al for the label of O'Connor et al because Campbell et al shows that the use of this chemiluminescent label in two-site assays provides a means of improving the sensitivity of measurement of proteins and polypeptides by one to two orders of magnitude.

Response to Arguments

11. Applicant's arguments filed June 6, 2005 have been fully considered but they are not persuasive.

Applicant's arguments directed to O'Connor only disclosing method of detecting a trophoblast disease in pregnant women is moot in view of the new rejections concerning Cole et al which specifically teaches diagnosis of trophoblastic disease in pregnant and non-pregnant subjects.

Applicant argues that Hochstrasser fails to provide the deficiencies apparent in O'Connor and fails to teach a step of confirming a subject is not pregnant. This is not found persuasive because Examiner has not relied upon Hochstrasser for teaching confirming a subject is not pregnant, but rather has relied upon Hochstrasser for teaching that it is known in the art that if analytes are known to be elevated in more than one condition. One must rule out one of the conditions to positively confirm which condition causes the elevated analytes. Further Cole et al specifically teaches that that patients can be diagnosed with choriocarcinoma solely from a persistent positive hCG result, in the absence of a pregnancy.

Applicant argues that Birken '416 fails to provide the deficiencies apparent in O'Connor and Hochstrasser. Applicant further argues that Birken '416 discloses methods which comprise detecting a completely different and distinct antigen than those recited in the present claims. This is not found persuasive because Examiner has not relied upon Birken for teaching the antigen, but rather has relied upon Birken for teaching that it is known in the art to compare values taken from normal individuals to values obtained from testing subjects to determine if the test subject is abnormal.

Applicant argues that the numerical values recited in the present claims are more than just an optimum threshold and that the cited references do not provide any

disclosure or suggestion that would have led a person of ordinary skill in the art to combine the teachings of the references in the particular manner being presently claimed. This is not found persuasive because the use of thresholds and standards are known in the art and since Birken teaches the comparison to normal individuals to determine abnormal subjects. One of ordinary skill in the art would establish thresholds or cutoff levels in order to determine if a test subject is abnormal or not. And one of ordinary skill in the art would recognize that establishing these thresholds requires experimentation at different cutoff values and as described in the previous office action and as stated above the optimum threshold in this case 50th percentile can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. Further, Applicant has not provided any experimentation establishing the 50th percentile in non-pregnant women nor has Applicant provided any indication that the 50th percentile would provide unexpected results. Thus the combination of references teach establishing thresholds and it is well within the ordinary skill in the art to determine threshold levels.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary Counts
Examiner
Art Unit 1641
August 15, 2005

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